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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,206	01/02/2002	Jasper Rine	UOCB118456	1317

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EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,206	RINE ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/15/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Upon review of the Office action mailed 16 January 2004, it is apparent that the cited reference Fodor et al. is not of record. Two references by Fodor et al. that are of record are not the intended reference. The intended reference by Fodor et al. is made of record on a Form PTO 892 attached to this Office action. Because the intended reference by Fodor et al. was not properly cited in the previous Office action this Office action is a non-final Office action.

Oath/Declaration

2. The power of attorney filed 15 July 2004 is accepted.

Terminal Disclaimer

3. The terminal disclaimer filed on 15 July 2004 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 5,777,888 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claim 69 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 69 is drawn to data in computer readable memory which is not patentable subject matter (see MPEP 2106).

6. Applicant's arguments filed 15 July 2004 have been fully considered but they are not persuasive. The applicants state that the claim is drawn to data structure and to functional descriptive material. However, the claim is drawn to an output signal data structure database in computer memory that is not distinguished from data for reasons of record. The claim is not drawn to computer programs in computer memory, or to data that affects the function of a machine. The applicants have not shown how the claimed subject matter affects the function of a computer. The applicants contention that the data affects the data output of a computer processing the claimed database is not persuasive because the claimed subject matter does not affect how data is processed, just as a music data on a CD does not affect how data is processed by a CD player, see MPEP 2106 (IV) (b).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 38-53, 55-66, 68-83, and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gress et al. in view of Granelli-Piperno et al. in view of Fodor et al. (U.S. Patent No. 5,800,992).

The claims are drawn to a method of assay of the response of a living thing to a stimulus by use of an array of probes comprising a predetermined sequence of nucleotides to individual gene transcripts by comparing databases comprising results of hybridizations of labeled polynucleotides derived from cells either treated with different stimuli or unstimulated control cells, the database produced by the method, and methods of generating the database produced by the method. The responses are measured by converting an output signal to an electrical signal and then converting the electrical signal to a value in a database. In some embodiments at least 50% of the gene transcripts of the cell are assayed, the cells are human cells, the probes consist of 24-240 nucleotides, and the database is computer implemented. In some embodiments the probes are in an X and Y coordinate grid. In some embodiments the method is repeated for different stimuli.

Gress et al. shows throughout, and especially on page 609 and figure 3 a general method of assaying patterns of transcription by use of labeled cDNA from mouse, and human cells by

use of a cDNA X-Y coordinate grid array of probes. The array provides an optical signal of expression in an assayed human cell of individual genes in the cell. Gress et al. shows importing the resulting data via an electrical signal of a Phosphorimager to a computer implemented relational database on page 616. Gress et al. shows in the abstract that their high density array allows for the efficient assay of thousands of clones simultaneously. Gress et al. shows on page 612 that polyA control probes hybridize non-specifically to many array cDNA probes and that other cDNA probes in the array contained repetitive sequences that also caused non-specific hybridization. Gress et al. shows on page 616 that one strategy to avoid background non-specific hybridization is to use probes that lack polyA tails by use of modified primers. Gress et al. does not show subjection of assayed cells to different stimuli, or comparison of the transcriptional profile of cells that have received different stimuli, or assay of discrete portions of the complete number of genes of the cell, or use of probes with a predetermined sequence of nucleotides.

Granelli-Piperno et al. shows in figures 1-9 the effect of a variety of compounds on expression of genes of human cells. The tested compounds include cytokines, mitogens, cyclosporin A, and cycloheximide. The response is determined by the intensity of a film image on an autoradiograph. Granelli-Piperno et al. show that assay of expression of genes after treatment of cells with drugs allows a determination of the effect of the drug on individual gene expression and further serves to gain insights on the mechanism of action of the drug.

Fodor et al. shows throughout a method of making an array of polynucleotide probes of predetermined sequence by independent in situ stepwise synthesis of each oligonucleotide probe on the array. Fodor et al. shows in columns 32, lines 12-24 that their arrays may be used to map

the location of a molecule on a chromosomal map. Fodor et al. shows in column 35 that their procedure may be used to assay the developmental stage cells from which the assayed sample is derived. In column 78-79, Fodor et al. shows that their method may be used to assay developmental stages of cells by assay of their mRNA content.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Gress et al. by assaying cells that have received treatments with different drugs according to the method of Granelli-Piperno et al. because Granelli-Piperno et al. shows that such an analysis serves to gain insights on the mechanism of action of the drug. It would have been further obvious to assay additional numbers of genes as desired to determine the effect of a drug on additional genes. Regarding the size of the probes, it would have been obvious to use portions of a cDNA probe of Gress et al. because Gress et al. shows that many array probes suffer from non-specific hybridization due to repetitive sequences of polyA tracts and that the problem may be solved by use of shorter probes. It would have been further obvious to use an array of probes with a predetermined sequence as disclosed by Fodor et al. because Fodor et al. shows that such an array has the advantage of allowing the sequences detected in the sample to be mapped to a particular location of the genome of the organism sampled. Regarding the limitations of claims 71 and 72, it would be further obvious to one of skill in the art to perform simple mathematical comparisons of the levels in stimulated and control cells such as subtraction or division by the basal level to reveal the extent of change in the level of the assayed mRNA.

10. Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82, and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gress et al. in view of Granelli-Piperno et al. in view of Fodor et al. as applied to claims 38-53, 55-66, 68-83, and 85 above, and further in view of Watson et al.

The claims are drawn to assays utilizing fungal cells.

Watson et al. shows on pages 573-575 that yeast cells contain genes that are regulated by stimuli such as metabolites.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Gress et al. in view of Granelli-Piperno et al. in view of Fodor et al. as applied to claims 38-53, 55-66, 68-83, and 85 above by using yeast gene probes and cells because Watson et al. shows that yeast cells have genes that are regulated by stimuli.

11. Applicant's arguments filed 15 July 2004 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The applicants state that Gress et al. requires an unsequenced array element and therefore cannot be combined with Fodor et al. which shows a sequenced array element. However Gress et al. does not teach away from sequenced array elements. Gress et al. shows the desirability of

sequencing array elements in the abstract and throughout, and shows sequencing of those elements that hybridize to probes of interest. Gress et al. does not sequence all array elements in order to reduce labor involved in sequencing those elements that do not hybridize to probes of interest and are therefore elements that are not of interest. Fodor et al. shows throughout a method of preparing arrays in which the sequences of each element are predetermined and that synthesizes oligonucleotides in each array element with the intended sequence. Fodor et al. thereby obviates the necessity of subsequent sequencing of array elements of interest. The method of Fodor et al. is therefore an improvement over the method of Gress et al. because it eliminates the necessity of sequencing array elements that hybridize to probes.

The applicants state that Granelli-Piperno et al. does not employ an array and assays only a small number of genes. However Granelli-Piperno et al. does not teach away from analysis of large numbers of genes, rather it analyzes the effect of a variety of stimulations of a cell on the expression of a desired number of genes. Granelli-Piperno was cited to show teaching to analyze gene expression in stimulated cells. Other elements of the claimed invention such as arrays of known sequences and storage of signals are shown in Gress et al. and Fodor et al. The applicants correctly note that Table 1 of Granelli-Piperno et al. does not show mRNA levels, but rather show protein or protein activity levels. Figures 1-9 of Granelli-Piperno et al. do show mRNA level analysis.

The applicants state that claims 63-65 and 80-82, drawn to analysis of particular percentages of the total number of genes in an organism, are not shown by the combination of references, particularly in view of the limited number of genes analyzed by Granelli-Piperno et

al. However none of the references teach away from analyzing large numbers of genes, and it would be obvious to analyze as many genes as desired because analysis of expression of any individual gene reveals whether stimuli regulates expression of that gene.

Double Patenting

12. The rejection of claims 38, 43-50, 56, 59, 62-65, 70, 74, 77, 79, and 80-82 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6, 13, 15, 16, 19, 26, and 28 of U.S. Patent No. 5,777,888 in view of Fodor et al. in the Office action mailed 16 January 2004 is withdrawn in view of the terminal disclaimer filed 15 July 2004.

Conclusion

13. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also

enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center at (800) 786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is (571) 272-0714. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J.S. Brusca 18 August 2004

John S. Brusca

Primary Examiner

Art Unit 1631

jsb